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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 03/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/758,893	BRYANT ET AL.	
	Examiner	Art Unit	
	Rebecca L. Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *9-13 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 14-19* is/are rejected.

7)☒ Claim(s) *1-8 and 14-19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *15 Jan 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-22 are currently pending in the instant application. Claims 9-13 and 20-22 are withdrawn from consideration as being for non-elected subject matter. Claims 1-8 and 14-19 are objected and rejected.

Election/Restrictions

Applicant's election with traverse of Group I and the further election of the product N-(1S-cyanomethylcarbamoyl-2-cyclohexylethyl)morpholine-4-carboxamide in the reply filed on 21 December 2004 is acknowledged. Upon further consideration as suggested by applicant, the examiner is including the claims 14-19 of Group III in with the elected invention of Group I. The traversal of the remainder of the restriction requirement is on the ground(s) that the requirement is improper based on MEPE 803 and that case law such as Harnisch supports applicants' position. This is not found persuasive because the restriction requirement is made under 35 U.S.C. 121. 35 U.S.C. 121 gives the Commissioner (Director) the authority to limit the examination of an application where two or more independent and distinct inventions are claimed to only one invention. The examiner has indicated that more than one independent and distinct invention is claimed in this application and has restricted (limited) claimed subject matter accordingly. Thus the requirement to restrict the claims in this application is predicated on the fact that the claimed subject matter involves more than one independent and distinct invention. Nowhere do applicants argue to the contrary. Nowhere do applicants point out and give reasons why the claims do not involve independent or distinct subject matter. So, here we have claims, which involve more

than one independent or distinct invention. Under 35 U.S.C. 121, the claims may be restricted and the examination limited to a restricted invention. Applicants' traversal of the restriction requirement is based on its intra-claim restriction. Again, it is noted that the restriction requirement here is predicated on the premise that the various compounds involved (i.e. the elected and non-elected compounds) differ in structure and element so much so as to be patentably distinct, i.e.., a reference which anticipated but the elected compounds claimed would not even render obvious the others. Furthermore, applicant has argued a lack of unity standard, which does not address the premise of the restriction requirement. Notwithstanding that lack of unity is not the basis for this restriction requirement, a lack of unity standard requires that the claims contain a special technical feature that defines a contribution over the art. Here the claims are directed to products which do not define a contribution over the art as can be seen by the various art rejections that follow. Also, there has been no rejection made under improper Markush groups so In re Harnisch, cited by applicants, is not relevant here. So, here we have claims which involve more than one independent or distinct inventions. Under 35 USC 121, the claims may be restricted and the examination limited to a restricted invention. Accordingly, the requirement to restrict is considered proper and is maintained .

Therefore, as stated on page 4 of the restriction requirement: **The elected invention for search and examination is**: The products of the **formula (I)** in which **R1** is a group of formula (a) wherein:

X1 is –C(O)-;

R5 is hydrogen or (C1-6)alkyl;

R7 is hydrogen or (C1-6)alkyl;

R9 is (i), (ii) or a group selected from (C3-12)cycloalkyl(C0-6)alkyl, (C6-12)aryl(C0=6)alkyl, (C9-12)polycycloaryl(C0=6)alkyl, wherein said cycloalkyl, aryl or polycycloaryl ring optionally is substituted by a group selected from -R16, -X4OR16, -X4SR16, -X4S(O)R16, -X4S(O2)R16,

$-X^4C(O)R^{16}$, $-X^4C(O)OR^{16}$, $-X^4OC(O)R^{16}$, $-X^4NR^{16}R^{17}$, $-X^4NR^{17}C(O)R^{16}$, $-X^4NR^{17}C(O)OR^{16}$, $-X^4C(O)NR^{16}R^{17}$, $-X^4S(O)_2NR^{16}R^{17}$, $-X^4NR^{17}C(O)NR^{16}R^{17}$ or

-X4NR17C(NR17)NR16R17 and wherein R9 within R9 any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C1-6)alkyl, (C1-6)alkylidene,

cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4P(O)(OR^4)OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4OC(O)R^{13}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$ and –X4C(O)R13;

R2 is hydrogen or (C1-6)alkyl;

R3 is hydrogen or (C1-6)alkyl;

R4 is (i) or a group selected from (C3-12)cycloalkyl(C0-6)alkyl, (C6-12)aryl(C0=6)alkyl and (C9-12)polycycloaryl(C0=6)alkyl, wherein said cycloalkyl, aryl or polycycloaryl ring optionally is substituted by a group selected from -R16, -X4OR16, -X4SR16, -X4S(O)R16, -X4S(O2)R16,

$-X^4C(O)R^{16}$, $-X^4C(O)OR^{16}$, $-X^4OC(O)R^{16}$, $-X^4NR^{16}R^{17}$, $-X^4NR^{17}C(O)R^{16}$, $-X^4NR^{17}C(O)OR^{16}$, $-X^4C(O)NR^{16}R^{17}$, $-X^4S(O)_2NR^{16}R^{17}$, $-X^4NR^{17}C(O)NR^{16}R^{17}$ or

-X4NR17C(NR17)NR16R17;

R11 is X5X6R18 wherein within R11 any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C1-6)alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted (C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4P(O)(OR^3)OR^{12}$, -X4OP(O)(OR3)OR12, -X4OC(O)R13, -X4NR12C(O)R13, -X4S(O)R13, -X4S(O)2R13 and –X4C(O)R13;

X3 is (C1-6)alkylene;

R12 at each occurrence independently is hydrogen, (C1-6)alkyl or halo-substittued (C1-3)alkyl;

R13 is (C1-6)alkyl or halo-substituted (C1-3)alkyl;

R14 is (C3-12)cycloalkyl(C0-6)alkyl, (C6-12)aryl(C0-6)alkyl, (C9-12)polycycloaryl(C0-6)alkyl, and wherein within R14 said cycloalkyl, aryl or polycycloaryl ring optionally is substituted by a group selected from -R16, -X4OR16, -X4SR16, -X4S(O)R16, -X4S(O2)R16, $-X^4C(O)R^{16}$, $-X^4C(O)OR^{16}$, $-X^4OC(O)R^{16}$, $-X^4NR^{16}R^{17}$, $-X^4NR^{17}C(O)R^{16}$, $-X^4NR^{17}C(O)OR^{16}$, $-X^4C(O)NR^{16}R^{17}$, $-X^4S(O)_2NR^{16}R^{17}$, $-X^4NR^{17}C(O)NR^{16}R^{17}$ or -X4NR17C(NR17)NR16R17;

R15 is hydrogen or (C1-6)alkyl;

X4 is a bond or (C1-6)alkylene;

R16 is hydrogen or (C1-6)alkyl;

R17 is (C3-12)cycloalkyl(C0=6)alkyl, (C6-12)aryl(C0-6)alkyl, (C9-12)polycycloaryl(C0-6)alkyl;

X5 is –C(O);

X6 is a bond;

R18 is morpholinyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomersl and the pharmaceutically acceptable salts thereof and the compounds of the **formula (II)** wherein the definitions of R2, R3, R4, R5, R9, R7 and R11 are only the definitions as found in claim 14 which fall within the scope of the definitions of the variables R2, R3, R4, R5, R9, R7 and R11 as defined above for the products of the formula (I); and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

The remaining subject matter of claims 1-8 and 14-19 that is not drawn to the above elected invention and the subject matter of claims 9-13 and 20-22 stands withdrawn under 37 CFR 1.142(b) as being for non-elected subject matter. The remaining compounds which are not within the elected invention, which are independent and distinct from the elected invention and do not have unity with the elected compound and are therefore withdrawn by means of a restriction requirement within the claims are, for example, the compounds of the formula (I) wherein R1 is the formula (b); X1 and X2 are –CH2S(O)2-;R14, R17, R9 or R10, R20, R4 are hetero(C3-12)cycloalkyl(C0-6)alkyl, hetero(C5-12)aryl(C0-6)alkyl or hetero(C8-12)polycycloarylC(0-6)alkyl R9 taken together with R7 and/or R10 taken together with R8; X5 is –C(O)C(O)or –S(O)2; X6 is –

O- or NR19; R4 and R2 are taken together or R4 and R3 tegoether with the carbon atom are taken together, etc

The above mentioned withdrawn compounds which are withdrawn from consideration as being for nonelected subject matter differ materially in structure and composition from the compounds of the elected invention. The withdrawn compounds differ from those of the elected invention, such as by furanyl, thienyl, piperidinyl, piperazinyl, and oxazole, etc. which are chemically recognized to differ in structure and function. This recognized chemical diversity of the compounds can be seen by the various classification of these compounds in the U.S. classification system, i.e. class 549 subclass (200)+ furanyl, class 549 subclass (1)+ thienyl,, class 548 subclass (215)+ oxazole, class 544 subclass 358(+) piperazinyl, etc. Therefore, again, the compounds which are withdrawn from consideration as being for non-elected subject matter differ materially in structure and composition and have been restricted properly as a reference which anticipated but the elected subject matter would not even render obvious the non-elected subject matter.

These withdrawn compounds are independent and distinct from the elected invention and do not have unity with the species elected and are therefor withdrawn by means of a restriction requirement within the claims.

The requirement is still deemed proper.

Claim Objections

Claims 3, 14, 15, 16 and 19 areobjected to because of the following informalities. Appropriate correction is required. At claim 3, page 109, lines 4-8, the phrase "and the

N-oxide... salts thereof" is repeated, and one of the two occurrences should be deleted. At claim 14, page 114, line 15, the conjunction "and" should be inserted before –X4S(O)2R13-. At claim 15, page 115, line 28; and claim 16, page 116, line 26; the conjunction "and" should be inserted before –X4SR12. At claim 19, page 11, line 2, a semicolon should be inserted at the end of the line.

Claims 15, 17 and 18 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 15, page 115, line 23, recites a possibility for R^9, i.e. $(C_{6\text{-}12})$aryl(C_0)alkyl, which is not embraced by the definition of R^9 in claim 14 upon which claim 15 depends. Claim 17 recites a possibility for R^{26}, i.e. $-C(O)OR^{12}$, which is not a permitted aromatic ring substituent as defined in claim 16, upon which claim 17 depends. Most of the possibilities for R^9 recited in claim 18 are not embraced by the definition of R^9 in claim 17 upon which claim 18 depends. The examiner recommends that Applicants review all of the dependent claims to make sure that all their recited definitions of the variables are embraced within the definitions of the variables in the claims upon which they depend.

Claims 7 and 19 are identical in scope. Upon an indication of allowability, one of these claims will be rejected over the other in accordance with the procedures of MPEP 706.03(k). In order to expedite prosecution of this application, it is recommended that one of these two claims be amended or canceled in the response to this Office action.

Claims 1-8 and 14-19 are objected to as containing non-elected subject matter. Claims 1-8 and 14-19 presented drawn solely to the elected invention for search and examination as identified above would appear free of this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 14-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for th compounds of the formulas (I) and (II) and their pharmaceutically acceptable salts thereof, does not reasonably provide enablement for the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers of the compounds of the formulas (I) and (II)..stereoisomers, tautomers and pharmaceutically acceptable salts of the compounds of the formula I and II. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,

7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

The nature of the invention is the compounds of the formula I or II and their N-oxide derivatives, protected derivatives, individual isomers and mixtures of isomers, and pharmaceutically acceptable salts thereof.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that an isomer is any compound having the same composition, including constitutional isomers, which are compounds whose atoms are connected differently and stereoisomers. Constitutional isomers can contain different functional groups in varying positions. Prodrugs are inactive substances that are converted to a drug within the body by enzymes or other chemicals. Prodrugs can be formed by various mechanisms and vary depending on the functional groups present in the parent compound, i.e. different prodrugs would arise from parent compounds containing varying functional groups, such as a carboxylic acid, an alcohol or an amine, all of which would require differing mechanisms. The term "derivative" found in the claims is defined as a compound, usually organic obtained from another compound by a simple chemical process or an organic compound containing a structural radical similar to that from which it is derived (Hackh's chemical dictionary, 1972). Therefore, the term "derivative" found in the claims renders the claims indefinite because it is unclear what compounds are being claimed, i.e. what similar radical is found in the derivative of hydroxamic acid of the formula (I) and encompassed by the instant claims

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is for the compounds of the formulas I and II, their stereoisomers, and pharmaceutically acceptable salts of the compounds. There is no data present in the instant specification for an alternate definition to the term derivative, not the preparation of constitutional isomers, or derivatives of prodrugs or protected derivatives of the instant compounds of the formulas I and II.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically, the instant claims include any isomer, i.e. any compound with the same number of each atom and any covalently bonded compound that would release the active parent compound along with any compound containing a structural radical similar to that from the compounds of the formulas (I) and (II).

The quantity or experimentation needed and the level of skill in the art

While the level of the skill in the pharmaceutical arts is high, it would require undue experimentation of one of ordinary skill in the art to prepare any isomer, derivative, or prodrug of the formulas I and II as instantly claimed since an isomer of the compounds of the formula I and II need only have the same composition of atoms, not necessarily the same order of atoms and can have varying functional groups in varying positions. The same applies to prodrugs since it would also require undue experimentation to prepare any covalently bonded compound that would release the

active parent drug since prodrugs are formed by varying mechanisms and depend on the functional groups of the parent compound. The only guidance present in the instant specification is for the compounds of the formulas I and II, their stereoismers and pharmaceutically acceptable salts thereof. There is no guidance or working examples present for constitutional isomers, prodrugs or derivatives of the formulas I or II. Therefore, the claims lack enablement and this rejection can be overcome by deleting the phrase "and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers;" from the instant claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8 and 14-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5 and 6 of U.S. Patent No. 6,455,502. Although the conflicting claims are not identical, they are not patentably distinct from each other because: Claims 5 and 6 of US Patent No. 6,455,502 anticipate and therefore render claims 1-8 and 14-19 as rejected under obvious-type double patenting since conflicting claim 5 claims the compounds :

N-[1R-cyanomethylcarbamoyl-2-(2-nitrobenzylsulfanyl) ethyl]morpholine-4-carboxamide ;

N-[1R-cyanomethylcarbamoyl-2-(2-cyanobenzylsulfanyl)ethyl]morpholine-4-carboxamide; ; and

N-[1R-cyanomethylcarbamoyl-2-(2-methylbenzylsulfanyl)ethyl]morpholine-4-carboxamide; and which correspond to specific compounds found in applicants instant claim 7 and the compounds of claims 1-6 and pharmaceutical compositions of claim 8 wherein R1 is a group of formula (a) wherein X1 is –C(O), R3 and R4 are hydrogen, R5 is hydrogen, R7 is hydrogen, R11 is the group X5X6R18 wherien X5 is the group –C(O), X6 is a bond, R18 is morpholinyl and R9 is the group nitrobenzylsulfanylmethyl, cyanobenzylsulfanylmethyl or 2-methyl benzylsulfanylmethyl and conflicting claim 6 is a pharmaceutical composition of conflicting claim 1, which includes the above mentioned compounds. This anticipates

applicants' instant claims since this disclosure of conflicting claims 5 and 6 is fully encompassed by applicants instant claims 1-8 and 14-19.

Claim Rejections - 35 USC § 102

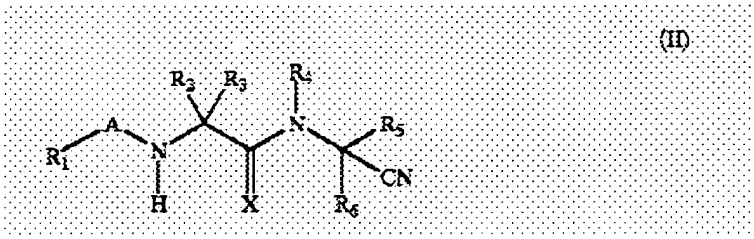
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

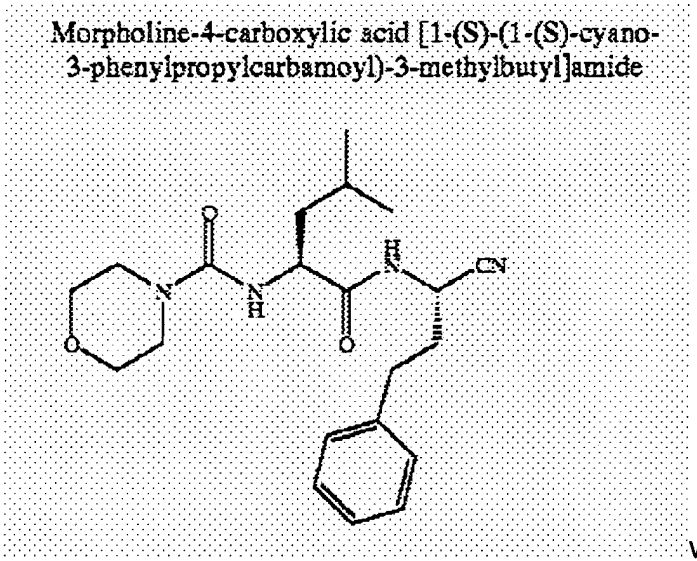
The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,395,897.

US Patent NO. 6,395,897 discloses the compounds of the formula II (col 68) and their pharmaceutical compositions (claim 17):

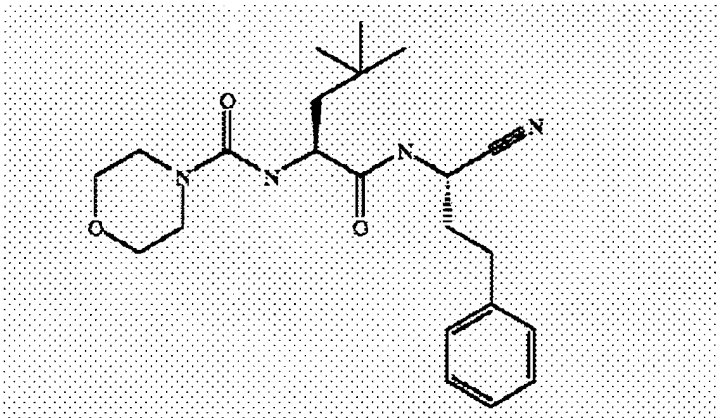


, specifically, for example, the compounds of (column 130) and claim 12:



which corresponds to applicants instant invention wherein R1 is a group of Formula (a), X1 is –C(O), R3 is hydrogen, R4 is a group (C6-12)aryl(C0-6)alkyl, R2 is hydrogen, R5 is hydrogen, R9 is (C1-6)alkyl, R7 is hydrogen and R11 is X5X6R18 wherein X5 is –C(O), X6 is a bond and R18 is morpholinyl;

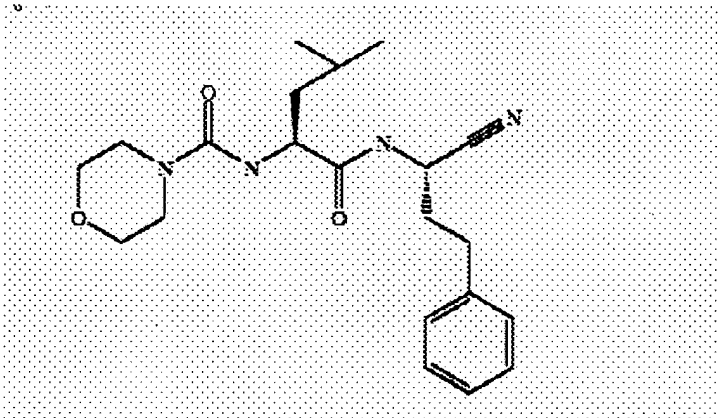
US Patent NO. 6,395,897 discloses the compound (column 163, claim 12)



N-(4-morpholinecarbonyl)-L-(4-methyl)leucine (1S-cyano-3-phenylpropyl)amide;

which corresponds to applicants instant invention wherein R1 is a group of formula (a), X1 is –C(O), R3 is hydrogen, R4 is a group (C6-12)aryl(C0-6)alkyl, R7 is hydrogen and R11 is X5X6R18 wherein X5 is –C(O), X6 is a bond and R18 is morpholinyl;

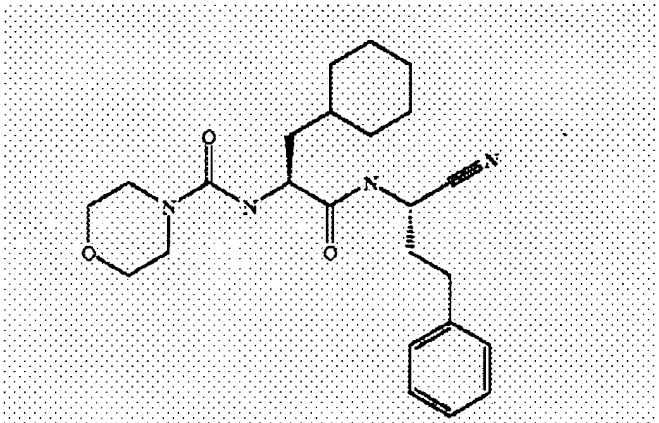
discloses the compound (column 168, claim 12)



N-(4-morpholylinecarbonyl)-L-leucine (1S-cyano-3-phenylpropyl)amide;

;

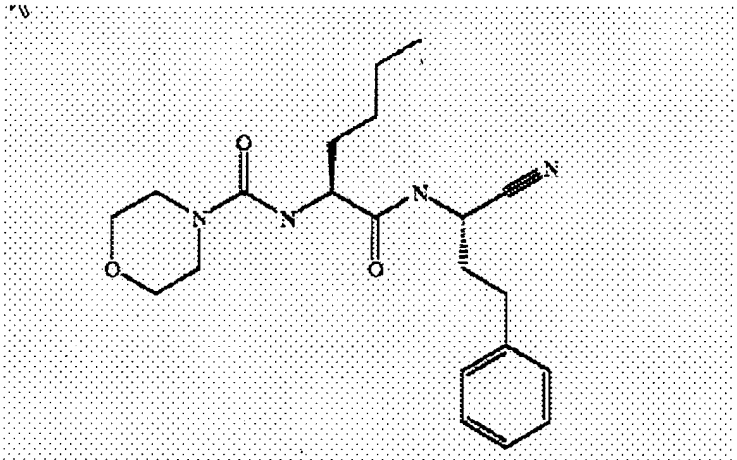
discloses the compound, column 169



N-(4-morpholinecarbonyl)-L-cyclohexylalanine (1S-cyano-3-phenylpropyl)amide;

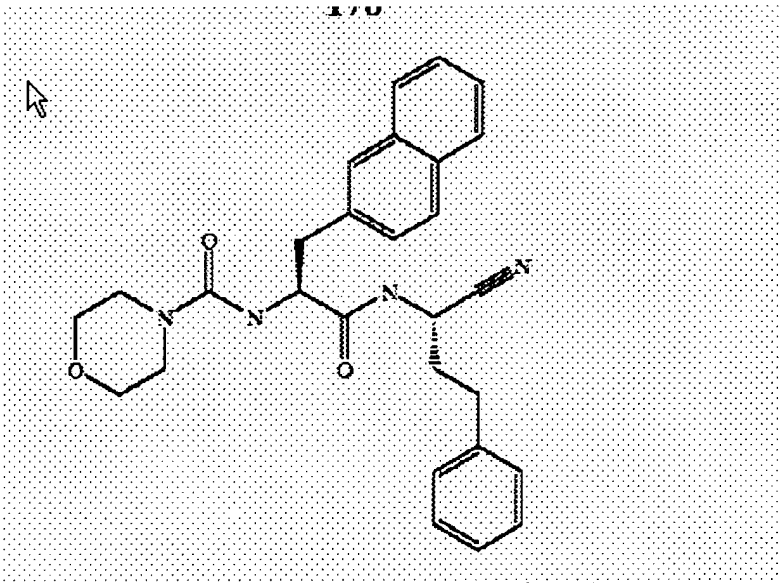
which corresponds to applicants instant invention wherein R9 is a group (C3-12)cycloalkyl(C0-6)alkyl;

discloses the compound, column 169

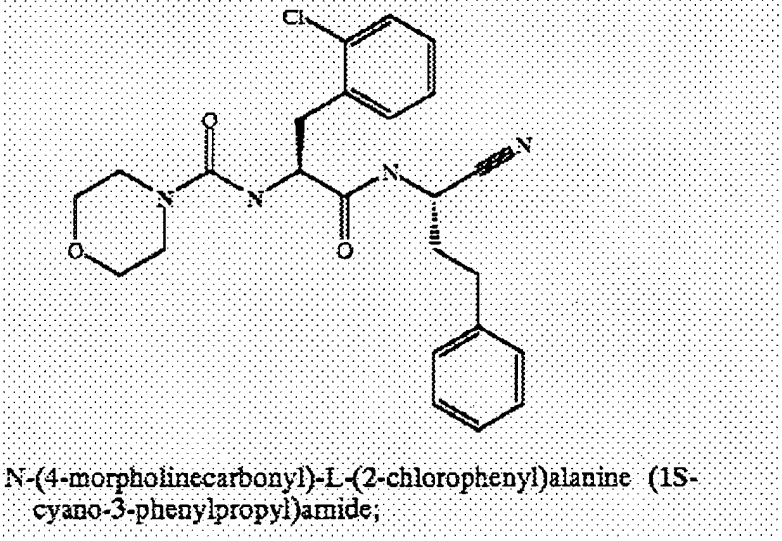


N-(4-morpholinecarbonyl)-L-nor-leucine (1S-cyano-3-phenylpropyl)amide;

discloses the compounds, column 170



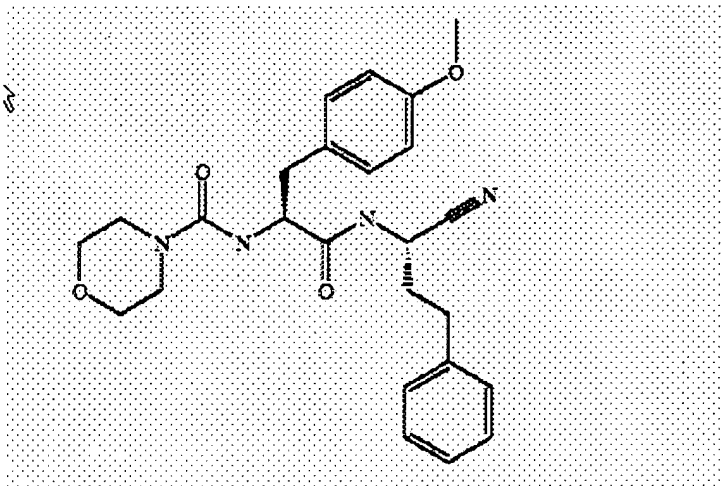
N-(4-morpholinecarbonyl)-L-(2-naphthyl)alanine (1S-cyano-3-phenylpropyl)amide;



N-(4-morpholinecarbonyl)-L-(2-chlorophenyl)alanine (1S-cyano-3-phenylpropyl)amide;

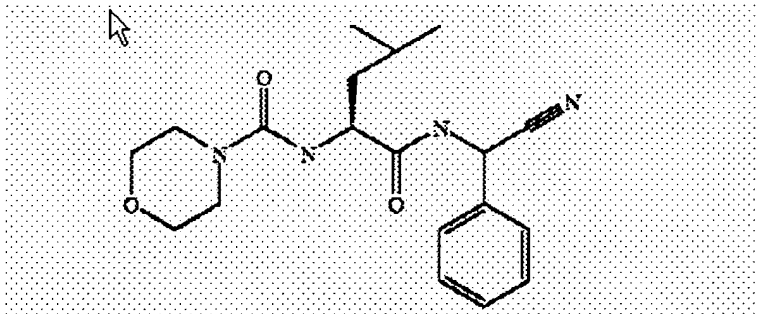
which correspond to applicants invention wherein R9 is (C6-12)aryl(C0-6)alkyl optionally substituted with a halo radical;

discloses the compound, column 170

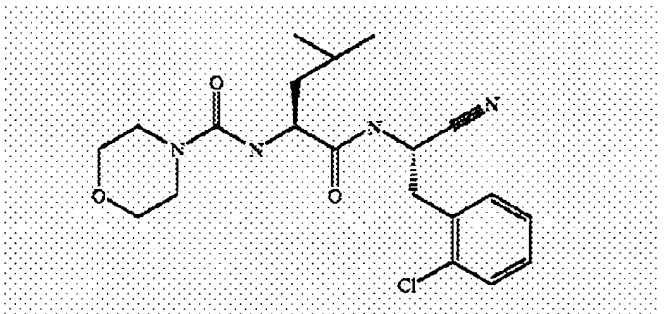


N-(4-morpholinecarbonyl)-L-(O-methyl)tyrosine (1S-cyano-3-phenylpropyl)amide;

discloses the compounds, column 172

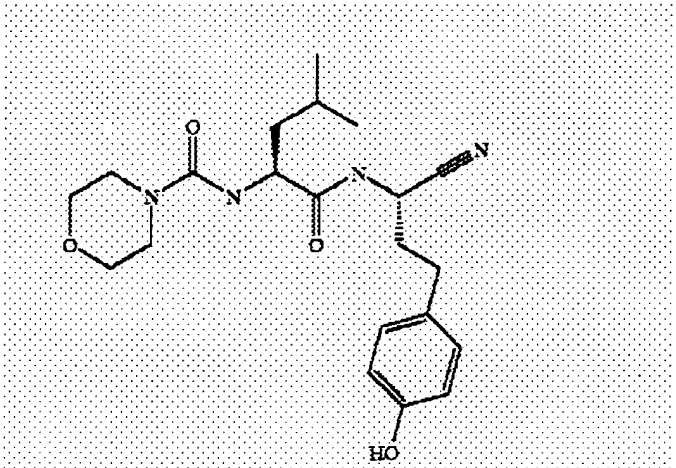


N-(4-morpholinecarbonyl)-L-leucine (1S-cyano-1-phenylmethyl)amide;



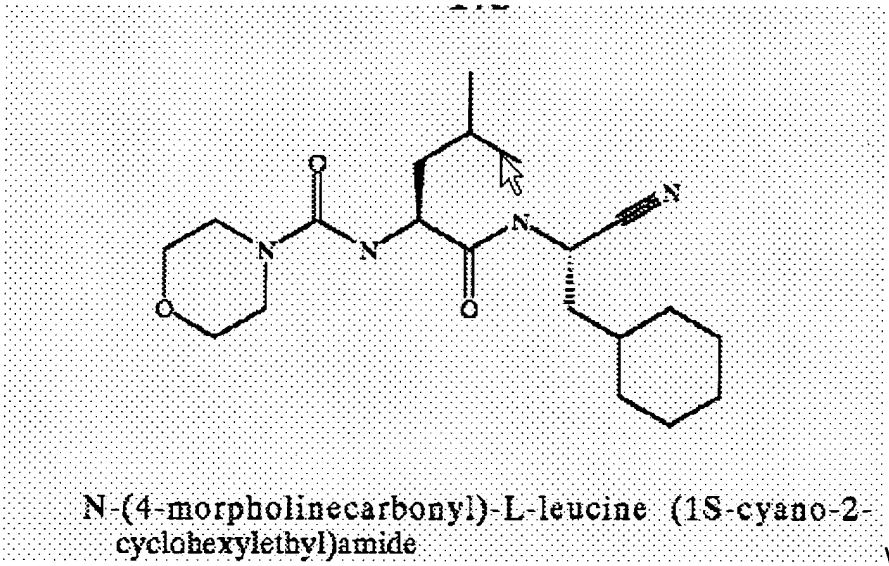
N-(4-morpholinecarbonyl)-L-leucine (1S-cyano-2-(2-chlorophenyl)ethyl)amide;

discloses the compound, column 172



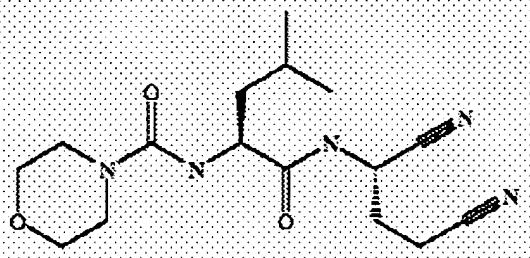
N-(4-morpholinecarbonyl)-L-leucine (1S-cyano-3-(4-hydroxyphenyl)propyl)amide;

discloses the compound, column 173

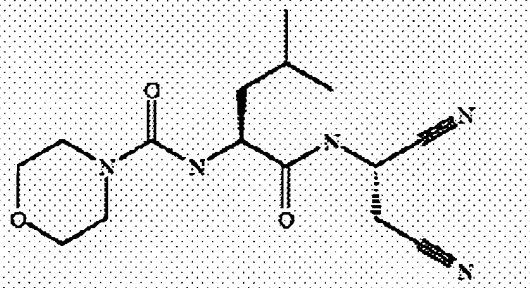


N-(4-morpholinecarbonyl)-L-leucine (1S-cyano-2-cyclohexylethyl)amide which corresponds to applicants invention wherein R4 is a group selected from (C3-12)cycloalkyl(C0-6)alkyl;

discloses the compounds, column 172



N-(4-morpholinecarbonyl)-L-leucine (1S,3-dicyanopropyl) amide;



N-(4-morpholinecarbonyl)-L-leucine (1S,2-dicyanoethyl) amide;

which correspond to applicants invention wherein R4 is (C1-6)alkyl, wherein aid alkyl optionally is substituted with cyano;

and claim 17 of US Patent NO. 6,395,897 claims:

> 17. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to claims 1 or 12.

which corresponds to applicants claim 8.

Claims 1-4 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by US patent No. 6,353,017 which discloses compounds which are inhibitors of cysteine proteases and are useful for the pharmaceutical treatment of diseases or medical

conditions in which cathepsins are implicated (column 1). The compounds found in US Patent NO. 6,353,017 which anticipate applicants instant claims are, for example, the compound # 156 found on column 67 which corresponds to applicants instant invention wherein R1 is the group of formula (a), X1 is –C(O), R3 is hydrogen, R5 is hydrogen, R7 is hydrogen, R2 is hydrogen, R4 is hydrogen, R9 is (C1-6)alkyl and R11 is X5X6R18 wherein X5 is –C(O), X6 is a bond and R18 is morpholinyl; and the compound # 191 found on column 75 which corresponds to applicants instant invention wherein R1 is a group of formula (a), R2 is hydrogen, R3 and R4 are hydrogen, R5 is hydrogen, R9 is a group (C3-12)cycloalkyl(C0-6)alkyl, R7 is hydrogen and R11 is the group X5X6R18 wherein X5 is –C(O), X6 is a bond and R18 is morpholinyl.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

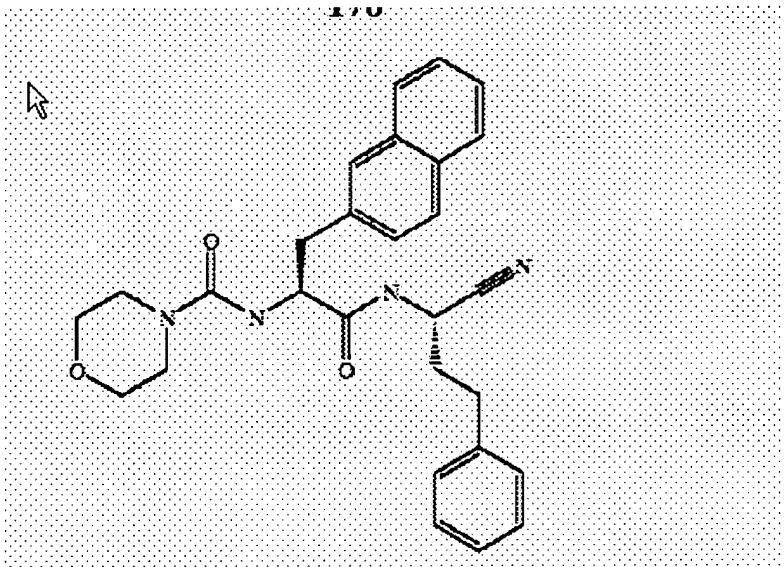
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

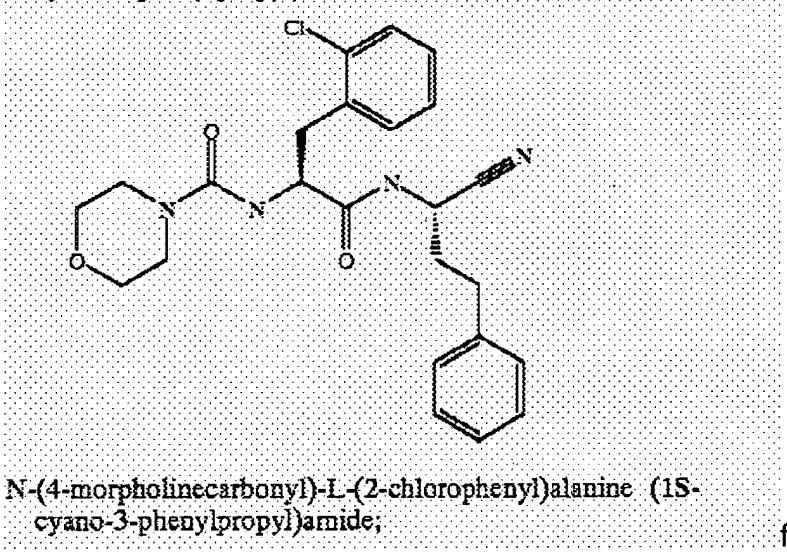
Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent NO. 6,395,897.

Determining the scope and contents of the prior art

US Patent NO. 6,395,897 discloses the compounds of the formula II/Iia which are useful as reversible inhibitors of the cysteine protease cathepsin S which are useful in the treatment of autoimmune diseases (column 1). Specifically, US Patent No. 6,395,897 discloses the compound formula II, column 68 wherein the position equivalent to applicants R4 can be, in the preferred compounds of formula II, H (column 86) and specific compounds which show a preference for the variables R4 and R9 are:



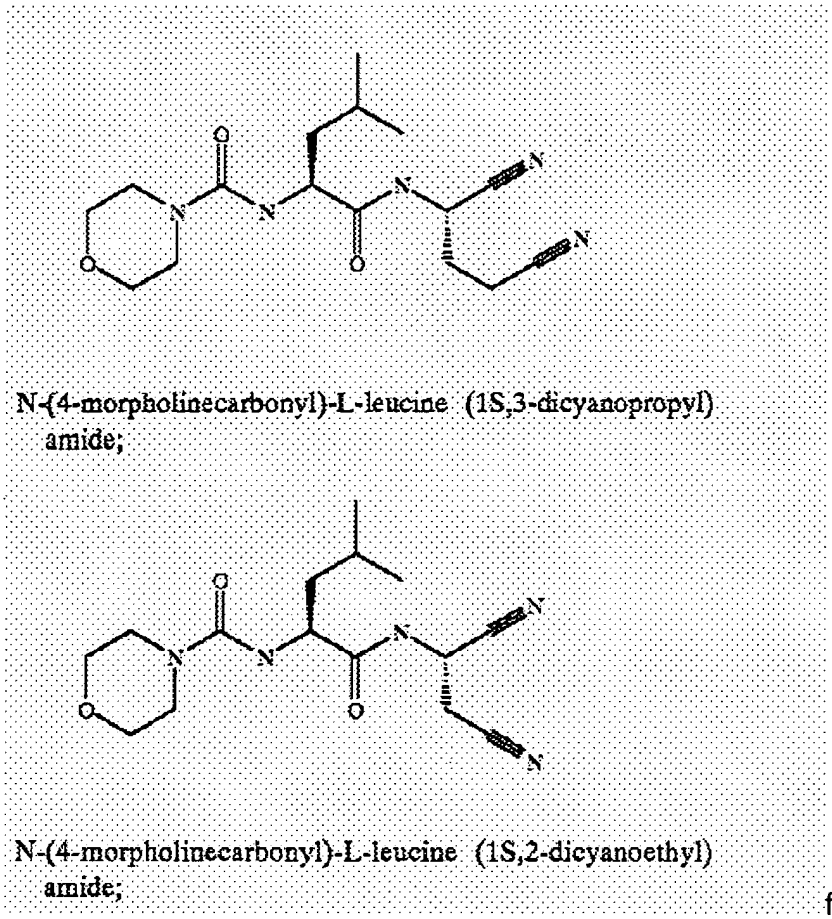
N-(4-morpholinecarbonyl)-L-(2-naphthyl)alanine (1S-cyano-3-phenylpropyl)amide;



N-(4-morpholinecarbonyl)-L-(2-chlorophenyl)alanine (1S-cyano-3-phenylpropyl)amide;

found in claim 12 wherein

R9 s C(6-12)aryl(C1-6)alkyl and the compounds:



N-(4-morpholinecarbonyl)-L-leucine (1S,3-dicyanopropyl) amide;

N-(4-morpholinecarbonyl)-L-leucine (1S,2-dicyanoethyl) amide;

found in claims 12 wherein R4 is alkyl optionally substituted with cyano.

Ascertaining the differences between the prior art and the claims at issue.

The difference between the prior art and the claims at issue is the combination of the substituent R9 on applicants instantly claimed compounds of claims 14 wherein R9 is C(6-12)aryl(C1-6)alkyl, such as benzyl optionally substituted with, for example halogen and R4 being hydrogen or C1-6 alkyl. The prior art compounds of formula (II) generically encompass applicants instantly claimed elected invention, however the prior art does not prepare a specific compound within applicants instant elected invention of claims 14. However, the prior art does prepare compounds which show preferences

towards the variables R4 as C1-6 alkyl substituted with cyano and does disclose specific compounds wherein R9 is C(6-12)aryl(c1-6)alkyl as shown above.

Resolving the Level of Ordinary Skill in the Art

However, minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention to prepare applicants instant invention wherein R9 is (C6-12)aryl(C1-6)alkyl optionally substituted by 1 to 5 radicals such as (C1-6)alkyl and halogen and R4 is hydrogen or C1-6 alkyl optionally substituted with cyano when faced with the prior art of US Patent No. 6395897 since the prior art discloses the compound of formula Ii which generically encompasses applicants instantly claimed compounds, since the prior art provides preferences in the form of formula II wherein the position equivalent to R4 is hydrogen and since the prior art provides specific compounds wherein R9 is C96-12)aryl(C1-6)alkyl and provides specific compounds wherein R4 is C1-6 alkyl optionally substituted with cyano. The motivation would be the high expectation of preparing additional compounds which are useful as pharmaceutical compositions for the treatment of autoimmune diseases.

Claims 14-16 are rejected under 35 USC 103(a) as being unpatentable over US Patent No. 6,353,017.

Determining the scope and contents of the prior art

US Patent NO. 6,353,017 discloses the compounds of the formula (I) column 2 which are inhibitors of cysteine proteases and are useful for the pharmaceutical treatment of diseases or medical conditions in which cathepsins are implicated (column 1). Specific compounds found in US Patent NO. 6,353,017 are, for example, the

compound # 156 found on column 67 which corresponds to applicants instant invention wherein R1 is the group of formula (a), X1 is –C(O), R3 is hydrogen, R5 is hydrogen, R7 is hydrogen, R2 is hydrogen, R4 is hydrogen, R9 is (C1-6)alkyl and R11 is X5X6R18 wherein X5 is –C(O), X6 is a bond and R18 is morpholinyl; and the compound # 191 found on column 75 which corresponds to applicants instant invention wherein R1 is a group of formula (a), R2 is hydrogen, R3 and R4 are hydrogen, R5 is hydrogen, R9 is a group (C3-12)cycloalkyl(C0-6)alkyl, R7 is hydrogen and R11 is the group X5X6R18 wherein X5 is –C(O), X6 is a bond and R18 is morpholinyl. Furthermore, US Patent No. 6,353,017 discloses the preferred compound formula III wherein the position equivalent to applicants R9 can be aryl-loweralkyl and the patent discloses specific compounds, for example, compounds #159, 216, 217, 219, 220-231, and 240-248 wherein the position equivalent to applicants instant R9 is benzyl optionally substituted with halogen or lower alkyl.

Ascertaining the differences between the prior art and the claims at issue.

The difference between the prior art and the claims at issue is the substituent R9 on applicants instantly claimed compounds of claims 14-16 wherein R9 is C(6-12)aryl(C1-6)alkyl, such as benzyl optionally substituted with, for example halogen. The prior art compounds of formula (I) generically encompass applicants instantly claimed elected invention, however the prior art does not prepare a specific compound within applicants instant elected invention of claims 14-17. However, the prior art does prepare compounds which show preferences towards the other variables, for example the compounds # 156 found on column 67 which corresponds to applicants instant

invention wherein R1 is the group of formula (a), X1 is –C(O), R3 is hydrogen, R5 is hydrogen, R7 is hydrogen, R2 is hydrogen, R4 is hydrogen, and R11 is X5X6R18 wherein X5 is –C(O), X6 is a bond and R18 is morpholinyl; and # 191 found on column 75 which corresponds to applicants instant invention wherein R1 is a group of formula (a), R2 is hydrogen, R3 and R4 are hydrogen, R5 is hydrogen, R7 is hydrogen and R11 is the group X5X6R18 wherein X5 is –C(O), X6 is a bond and R18 is morpholinyl. The only difference between these compounds and applicants instantly claimed elected invention is R9. However, the prior art provides numerous preferences for preparing compounds wherein the position equivalent to R9 benzyl optionally substituted with halo, see examples, column 7 wherein the more preferred formula III, R33 can be aryl-lower alkyl and the specific compounds # 159, column 61 (R9 is benzyl), examples 216, 217 and 219 wherein R9 is benzyl substituted with chlorine or methyl, and further examples 220-231 R9 is benzyl substituted with methyl and 240-248 wherein R9 is benzyl substituted with two chlorines.

Resolving the Level of Ordinary Skill in the Art

However, minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention to prepare applicants instant invention wherein R9 is (C6-12)aryl(C1-6)alkyl optionally substituted by 1 to 5 radicals such as (C1-6)alkyl and halogen when faced with the prior art of US Patent No. 6,353,017 since the prior art discloses the compound of formula I which generically encompasses applicants instantly claimed compounds, since the prior art provides preferences in the form of formula III wherein the position equivalent to R9 can be aryl-

lower alkyl and since the prior art provides compounds which differ only by the position R9 and provide preferences towards R9 as benzyl optionally substituted by lower alkyl and halogen. The motivation would be the high expectation of preparing additional compounds which are useful as pharmaceutical compositions for the treatment of diseases in which which cathepsins are implicated.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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